CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020759/020760

Trade Name: TROVAN TABLETS AND TROVAN I.V.

Generic Name: TROVAFLOXACIN MESYLATE AND ALATROFLOXACIN MESYLATE INJECTION

Sponsor: PFIZER CENTRAL RESEARCH

Approval Date: 12/18/97

Indication(s): TREATMENT OF INFECTIONS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: : 020759/020760

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020759/020760

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-759
NDA 20-760

20-759
20-760

DEC 18 1997

DEC 18 1997

Ronald I. Trust, Ph.D., M.B.A.
Associate Director
Regulatory Affairs - Liaison
Pfizer Central Research
Eastern Point Road
Groton, CT 06340

Dear Dr. Trust:

Please refer to your new drug applications (NDAs) submitted December 27, 1996 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TROVAN®Tablets (trovafloxacin mesylate) 100 mg and 200 mg, NDA 20-759; and TROVAN®I.V. (alatrofloxacin mesylate injection) 200 mg and 300 mg, NDA 20-760.

We acknowledge receipt of your amendments dated January 13, 20, and 28, February 10, March 17, April 3, 25, and 28, July 23, August 15 and 26, September 18, 22, and 25, October 9, 10, 13, 17, 21, 23, and 29, November 14, 19, 20, and 21, December 2, 3, 4, 5, 9, 11, and 12, 1997.

The user fee goal date is December 30, 1997.

We also acknowledge receipt of your letter dated October 13, 1997 requesting withdrawal of the

These new drug applications request approval of the following indications:

1. Nosocomial pneumonia
2. Community-acquired pneumonia
3. Acute bacterial exacerbation of chronic bronchitis
4. Acute sinusitis
5. Uncomplicated skin and skin structure infections
6. Complicated skin and skin structure infections, including diabetic foot infections
7. Complicated intra-abdominal infections, including post-surgical infections
8. Complicated gynecologic and pelvic infections, including post-surgical infections
9. Surgical prophylaxis - elective colorectal surgery
10. Surgical prophylaxis - elective abdominal and vaginal hysterectomy

11. Acute uncomplicated gonorrhea
12. Non-gonococcal urethritis and cervicitis
13. Bacterial prostatitis
14. Uncomplicated urinary tract infections including cystitis

16. Pelvic inflammatory disease

We have completed the review of these applications, including the submitted draft labeling as amended on December 18, 1997, and have concluded that adequate information has been presented to demonstrate that these drug products are safe and effective for use as recommended in the revised draft labeling dated December 18, 1997 (enclosed). Accordingly, these applications are approved effective on the date of this letter.

The data submitted are inadequate to support the use of TROVAN in the treatment of patients with

Before these indications may be approved, under 21 CFR 314.725(b)(5) and 314.126, you need to submit data from adequate and well controlled studies demonstrating that the drug is safe and effective for these uses.

The final printed labeling (FPL) for these drug products must be identical to the enclosed labeling. Marketing these products with FPL that is not identical to this labeling may render these products misbranded and unapproved new drugs.

Please submit 25 copies of the FPL to each application as soon as they are available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes these submissions should be designated **"FINAL PRINTED LABELING"** for approved **NDA 20-759, NDA 20-760.** Approval of these submissions by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of these drugs become available, revision of the labeling may be required.

We remind you of your Phase 4 commitments specified in your letter dated December 18, 1997. These commitments, along with any completion dates agreed upon, are listed below:

Protocols, data, and final reports should be submitted to the appropriate INDs for these products and a copy of the cover letter sent to the corresponding NDAs. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to these NDAs as correspondence. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to the appropriate applications (NDAs) a status summary of each commitment. The status summary should include information on each study, expected completion and submissions dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, resulting to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Special Pathogens and Immunologic Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the methods have not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of each drug product when available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314. 81.

If you have questions, please contact:

Ms. Pauline Fogarty
Regulatory Health Manager
(301) 827-2125

Sincerely yours,

/S/ 12.18.97

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020759/020760

FINAL PRINTED LABELING

(FINAL: 18-DEC-1997)
[insert package insert code here]

DEC 19 1997

APPROVED

TROVAN™ Tablets
(trovafloxacin mesylate)
TROVAN™ I.V.
(alatrofloxacin mesylate injection)
For Intravenous Infusion

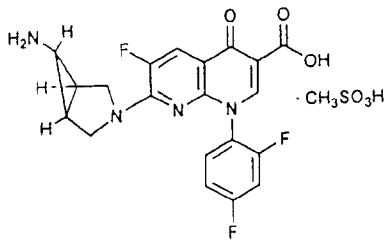
TROVAN is available as TROVAN Tablets (trovafloxacin mesylate) for oral administration and as TROVAN I.V. (alatrofloxacin mesylate injection), a prodrug of trovafloxacin, for intravenous administration.

DESCRIPTION

TROVAN Tablets

TROVAN Tablets contain trovafloxacin mesylate, a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, trovafloxacin mesylate, a fluoronaphthyridone related to the fluoroquinolone antibacterials, is (1α, 5α, 6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate. Trovafloxacin mesylate differs from other quinolone derivatives by having a 1,8-naphthyridine nucleus.

The chemical structure is:



Its empirical formula is $C_{20}H_{15}F_3N_4O_3 \bullet CH_3SO_3H$ and its molecular weight is 512.46.

Trovafloxacin mesylate is a white to off-white powder.
Trovafloxacin mesylate is available in 100 mg and 200 mg (trovafloxacin equivalent) blue, film-coated tablets. TROVAN Tablets contain microcrystalline cellulose, crosslinked sodium carboxymethylcellulose and magnesium stearate. The tablet coating is a mixture of hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol and FD&C blue #2 aluminum lake.

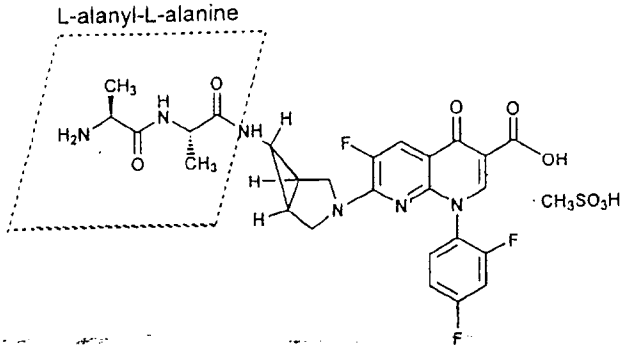
TROVAN I.V.

TROVAN I.V. contains alatrofloxacin mesylate, the L-alanyl-L-alanyl prodrug of trovafloxacin mesylate. Chemically, alatrofloxacin mesylate is (1α, 5α, 6α)-L-alanyl-*N*-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate. It is intended for administration by intravenous infusion.

Following intravenous administration, the alanine substituents in alatrofloxacin are rapidly hydrolyzed *in vivo* to yield trovafloxacin. (See **CLINICAL PHARMACOLOGY**)

The chemical structure is:

L-alanyl-L-alanine



Its empirical formula is $C_{26}H_{25}F_3N_6O_5 \bullet CH_3SO_3H$ and its molecular weight is 654.62.

Alatrofloxacin mesylate is a white to light yellow powder.

TROVAN I.V. is available in 40 mL and 60 mL single use vials as a sterile, preservative-free aqueous concentrate of 5 mg trovafloxacin/mL as alatrofloxacin mesylate intended for dilution prior to intravenous administration of doses of 200 mg or 300 mg of trovafloxacin, respectively. (See **HOW SUPPLIED.)**

The formulation contains Water for Injection, and may contain sodium hydroxide or hydrochloric acid for pH adjustment.
The pH range for the 5 mg/mL aqueous concentrate is 3.5 to 4.3.

CLINICAL PHARMACOLOGY

After intravenous administration, alatrofloxacin is rapidly converted to trovafloxacin. Plasma concentrations of alatrofloxacin are below quantifiable levels within 5 to 10 minutes of completion of a one hour infusion.

Absorption

Trovafloxacin is well-absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 88%. For comparable dosages, no dosage adjustment is necessary when switching from parenteral to oral administration (Figure 1). (See **DOSAGE AND ADMINISTRATION**.)

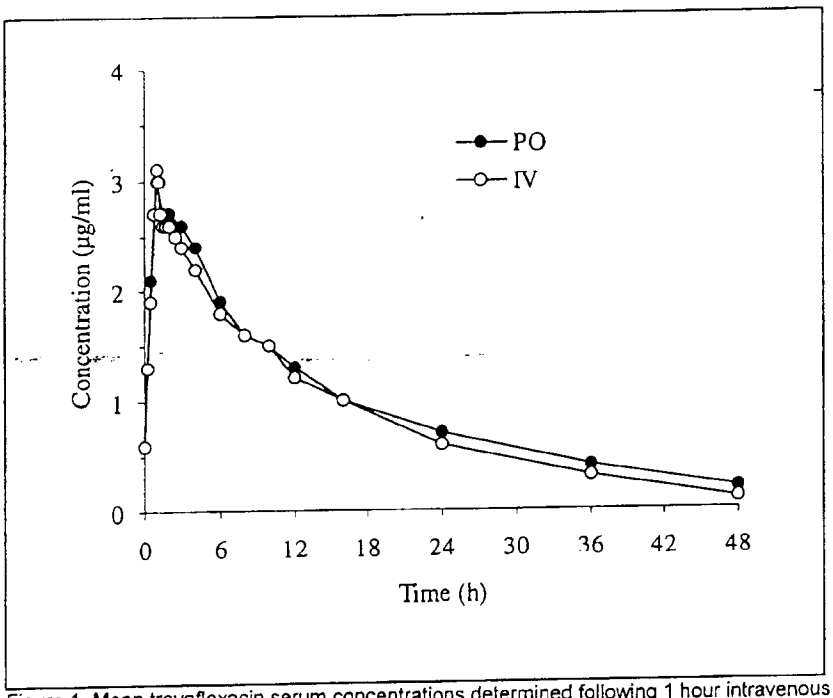


Figure 1. Mean trovafloxacin serum concentrations determined following 1 hour intravenous infusions of alatrofloxacin at daily doses of 200 mg (trovafloxacin equivalents) to healthy male volunteers and following daily oral administration of 200 mg trovafloxacin for seven days to six male and six female healthy young volunteers.

Pharmacokinetics

The mean pharmacokinetic parameters (±SD) of trovafloxacin after single and multiple 100 mg and 200 mg oral doses and one hour intravenous infusions of alatrofloxacin in doses of 200 and 300 mg (trovafloxacin equivalents) appear in the chart below.

TROVAFLOXACIN PHARMACOKINETIC PARAMETERS

	C_{max} (µg/mL)	T_{max} (hrs)	AUC[1,2] (µg•h/mL)	$T_{1/2}$ (hrs)	V_{dss} (L/Kg)	CL (mL/hr/Kg)	CL_r (mL/hr/Kg)
Trovafloxacin 100 mg							
Single dose	1.0±0.3	0.9±0.4	11.2±2.2	9.1	----	----	----
Multiple dose	1.1±0.2	1.0±0.5	11.8±1.8	10.5	----	----	----
Trovafloxacin 200 mg							
Single dose	2.1±0.5	1.8±0.9	26.7±7.5	9.6	----	----	----
Multiple dose	3.1±.1.0	1.2±0.5	34.4±5.7	12.2	----	----	----
Alatrofloxacin 200 mg*							
Single dose	2.7±0.4	1.0±0.0	28.1±5.1	9.4	1.2±0.2	93.0±17.4	6.5±3.5
Multiple dose	3.1±0.6	1.0±0.0	32.2±7.3	11.7	1.3±0.1	81.7±17.8	8.6±2.4
Alatrofloxacin 300 mg*							
Single dose	3.6±0.6	1.3±0.4	46.1±5.2	11.2	1.2±0.1	84.6±6.0	6.9±0.5
Multiple dose	4.4±0.6	1.2±0.2	46.3±3.9	12.7	1.4±0.1	84.5±11.1	8.4±1.8

*trovafloxacin equivalents

[1,2] Single dose: AUC(0-∞), multiple dose: AUC(0-24)

C_{max}= Maximum serum concentration; T_{max}=Time to C_{max}; AUC=Area under concentration vs. time curve, $T_{1/2}$=serum half-life; V_{ss}=Volume of distribution; Cl=Total clearance; Cl_r=Renal clearance

Serum concentrations of trovafloxacin are dose-proportional after oral administration of trovafloxacin in the dose range of 30 to 1000 mg or after intravenous administration of

alatrofloxacin in the dose range of 30 to 400 mg (trovafloxacin equivalents). Steady state concentrations are achieved by the third daily oral or intravenous dose of trovafloxacin with an accumulation factor of approximately 1.3 times the single dose concentrations.

Oral absorption of trovafloxacin is not altered by concomitant food intake; therefore, it can be administered without regard to food.

The systemic exposure to trovafloxacin ($AUC_{0-\infty}$) administered as crushed tablets via nasogastric tube into the stomach was identical to that of orally administered intact tablets. Administration of concurrent enteral feeding solutions had no effect on the absorption of trovafloxacin given via nasogastric tube into the stomach. When trovafloxacin was administered as crushed tablets into the duodenum via nasogastric tube, the $AUC_{0-\infty}$ and peak serum concentration (Cmax) were reduced by 30% relative to the orally administered intact tablets. Time to peak serum level (Tmax) was also decreased from 1.7 hrs to 1.1 hrs..

Distribution

The mean plasma protein bound fraction is approximately 76%, and is concentration-independent. Trovafloxacin is widely distributed throughout the body. Rapid distribution of trovafloxacin into tissues results in significantly higher trovafloxacin concentrations in most target tissues than in plasma or serum.

Fluid or Tissue	Tissue-Fluid/-Serum Ratio* (Range)
Respiratory	
bronchial macrophages (multiple dose)	24.1 (9.6-41.8)
lung mucosa	1.1(0.7-1.5)
lung epithelial lining fluid (multiple dose)	5.8 (1.1-17.5)
whole lung	2.1 (0.42-5.03)
Skin, Musculoskeletal	
skin	1.0 (0.20-1.88)
subcutaneous tissue	0.4 (0.15-0.68)
skin blister fluid	0.7-0.9 (blister/plasma)
skeletal muscle	1.5 (0.50-2.90)
bone	1.0 (0.55-1.67)
Gastrointestinal	
colonic tissue	0.7 (0.0-1.47)
peritoneal fluid	0.4 (0.0-1.25)
bile	15.4 (11.9-21.0)
Central Nervous System	
cerebrospinal fluid (CSF), adults	0.25 (0.03-0.33)
cerebrospinal fluid (CSF), children	0.28**
Reproductive	
prostatic tissue	1.0 (0.5-1.6)
cervix (multiple dose)	0.6 (0.5-0.7)
ovary	1.6 (0.3-2.2)
fallopian tube	0.7 (0.2-1.1)
myometrium (multiple dose)	0.6 (0.4-0.8)
uterus	0.6 (0.3-0.8)
vaginal fluid (multiple dose)	4.7 (0.8-20.8)

* Mean values in adults over 2-29 hours following drug administration, except individual lung tissues, which were single time points of 6 hours following drug administration

** Ratio of composite AUC(0-24) in CSF/composite AUC(0-24) in serum in 22 pediatric patients aged 1 to 12 years after 1 hour i.v. infusion of single dose alatrofloxacin (equivalent trovafloxacin dose range: 4.5-9.9 mg/kg)

Presence in Breast Milk

Trovafloxacin was found in measurable concentrations in the breast milk of three lactating subjects. The average measurable breast milk concentration was 0.8 μg/mL (range: 0.3-2.1 μg/mL) after single i.v. alatrofloxacin (300 mg trovafloxacin equivalents) and repeated oral trovafloxacin (200 mg) doses.

Metabolism

Trovafloxacin is metabolized by conjugation (the role of cytochrome P_{450} oxidative metabolism of trovafloxacin is minimal). Thirteen percent of the administered dose appears in the urine in the form of the ester glucuronide and 9% appears in the feces as the N-acetyl metabolite (2.5% of the dose is found in the serum as the active N-acetyl metabolite). Other minor metabolites (diacid, sulfamate, hydroxycarboxylic acid) have been identified in both urine and feces in small amounts (<4% of the administered dose)..

Excretion

Approximately 50% of an oral dose is excreted unchanged (43 % in the feces and 6% in the urine).

After multiple 200 mg doses, to healthy subjects, mean (± SD) cumulative urinary trovafloxacin concentrations were 12.1 ±3.4 μg/mL. With these levels of trovafloxacin in urine, crystals of trovafloxacin have not been observed in the urine of human subjects.

Special Populations

Geriatric

In adult subjects, the pharmacokinetics of trovafloxacin are not affected by age (range 19-78 years).

Pediatric

Limited information is available in the pediatric population (See **Distribution**). The pharmacokinetics of trovafloxacin have not been fully characterized in pediatric populations less than 18 years of age.

Gender

There are no significant differences in trovafloxacin pharmacokinetics between males and females when differences in body weight are taken into account. After single 200 mg doses, trovafloxacin Cmax and AUC(0-∞) were 60% and 32% higher, respectively, in healthy females compared to healthy males. Following repeated daily administration of 200 mg for 7 days, the Cmax for trovafloxacin was 38% higher and AUC(0-24) was 16% higher in healthy females compared to healthy males. The clinical importance of the increases in serum levels of trovafloxacin in females has not been established. (See **PRECAUTIONS: Information for Patients**).

Chronic Hepatic Disease

Following repeated administration of 100 mg for 7 days to patients with mild cirrhosis (Child-Pugh Class A), the AUC(0-24) for trovafloxacin was increased ~45% compared to matched controls. Repeated administration of 200 mg for 7 days to patients with moderate cirrhosis (Child-Pugh Class B) resulted in an increase of ~50% in AUC(0-24) compared to matched controls. There appeared to be no significant effect on trovafloxacin Cmax for either group. The oral clearance of trovafloxacin was reduced ~30% in both cirrhosis groups, which corresponded to prolongation of half-life by 2-2.5 hours (25-30% increase) compared to

controls. There are no data in patients with severe cirrhosis (Child-Pugh Class C). Dosage adjustment is recommended in patients with mild to moderate cirrhosis. (See **DOSAGE AND ADMINISTRATION**)

Renal Insufficiency
The pharmacokinetics of trovafloxacin are not affected by renal impairment. Trovafloxacin serum concentrations are not significantly altered in subjects with severe renal insufficiency (creatinine clearance < 20 mL/min), including patients on hemodialysis.

Photosensitivity Potential
In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy volunteers (12 per group), the minimum erythematous dose (MED) was measured for ciprofloxacin, lomefloxacin, trovafloxacin and placebo before and after drug administration for 5 days. In this study, trovafloxacin (200 mg q.d.) was shown to have a lower potential for producing delayed photosensitivity skin reactions than ciprofloxacin (500 mg b.i.d.) or lomefloxacin (400 mg q.d.), although greater than placebo. (See **PRECAUTIONS: Information for Patients**)

Drug-drug Interactions
The systemic availability of trovafloxacin following oral tablet administration is significantly reduced by the concomitant administration of antacids containing aluminum and magnesium salts, sucralfate, vitamins or minerals containing iron, and concomitant intravenous morphine administration.

Administration of trovafloxacin (300 mg p.o.) 30 minutes after administration of an antacid containing magnesium hydroxide and aluminum hydroxide resulted in reductions in systemic exposure to trovafloxacin (AUC) of 66% and peak serum concentration (Cmax) of 60%. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION**)

Concomitant sucralfate administration (1g) with trovafloxacin 200 mg p.o. resulted in a 70% decrease in trovafloxacin systemic exposure (AUC) and a 77% reduction in peak serum concentration (Cmax). (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION**)

Concomitant administration of ferrous sulfate (120 mg elemental iron) with trovafloxacin 200 mg p.o. resulted in a 40% reduction in trovafloxacin systemic exposure (AUC) and a 48% decrease in trovafloxacin Cmax. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION**)

Concomitant administration of intravenous morphine (0.15 mg/kg) with oral trovafloxacin (200 mg) resulted in a 36% reduction in trovafloxacin AUC and a 46% decrease in trovafloxacin Cmax. Trovafloxacin administration had no effect on the pharmacokinetics of morphine or its pharmacologically active metabolite, morphine-6-β-glucuronide. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION**)

Minor pharmacokinetic interactions that are most likely without clinical significance include calcium carbonate, omeprazole and caffeine.

Concomitant administration of calcium carbonate (1000 mg) with trovafloxacin 200 mg p.o. resulted in a 20% reduction in trovafloxacin AUC and a 17% reduction in peak serum trovafloxacin concentration (Cmax).

A 40 mg dose of omeprazole given 2 hours prior to trovafloxacin (300 mg p.o.) resulted in a 17% reduction in trovafloxacin AUC and a 17% reduction in trovafloxacin peak serum concentration (Cmax).

Administration of trovafloxacin (200 mg) concomitantly with caffeine (200 mg) resulted in a 17% increase in caffeine AUC and a 15% increase in caffeine Cmax. These changes in caffeine exposure are not considered clinically significant.

No significant pharmacokinetic interactions include cimetidine, theophylline, digoxin, warfarin and cyclosporine.

Cimetidine co-administration (400 mg twice daily for 5 days) with trovafloxacin (200 mg p.o. daily for 3 days) resulted in changes in trovafloxacin AUC and Cmax of less than 5%.

Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with theophylline (300 mg twice daily for 14 days) resulted in no change in theophylline AUC and Cmax.

Trovafloxacin (200 mg p.o. daily for 10 days) co-administration with digoxin (0.25 mg daily for 20 days) did not significantly alter systemic exposure (AUC) to digoxin or the renal clearance of digoxin.

Trovafloxacin (200 mg p.o. daily for 7 days) does not interfere with the pharmacokinetics nor the pharmacodynamics of warfarin (daily for 21 days). Concomitant oral administration of trovafloxacin did not affect the systemic exposure (AUC) or peak plasma concentrations (Cmax) of the S or R isomers of warfarin, nor did it influence prothrombin times.

Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with cyclosporine (daily doses from 150-450 mg for 7 days) resulted in decreases of 10% or less in systemic exposure to cyclosporine (AUC) and in the peak blood concentrations of cyclosporine.

Microbiology

Trovafloxacin is a fluoronaphthyridone related to the fluoroquinolones with *in vitro* activity against a wide range of gram-negative and gram-positive aerobic, and anaerobic microorganisms. The bactericidal action of trovafloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. Mechanism of action of fluoroquinolones including trovafloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between trovafloxacin and the mentioned classes of antibiotics. The overall results obtained from *in vitro* synergy studies, testing combinations of trovafloxacin with beta-lactams and aminoglycosides, indicate that synergy is strain specific and not commonly encountered. This agrees with results obtained previously with other fluoroquinolones. Resistance to trovafloxacin *in vitro* develops slowly via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to trovafloxacin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10}. Although cross-resistance has been observed between trovafloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to trovafloxacin.

Trovafloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes
Viridans group streptococci

Aerobic gram-negative microorganisms
Escherichia coli
Gardnerella vaginalis
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa

Anaerobic microorganisms
Bacteroides fragilis
Peptostreptococcus species
Prevotella species

Other microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown**.

Trovafloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤2 µg/mL against most (90%) strains of the following microorganisms; however, the safety and effectiveness of trovafloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative microorganisms
Citrobacter freundii
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris

Anaerobic microorganisms

Bacteroides distasonis
Bacteroides ovatus
Clostridium perfringens

Other microorganisms
Mycoplasma hominis
Ureaplasma urealyticum

NOTE: *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* complex organisms are commonly resistant to trovafloxacin.
NOTE: The activity of trovafloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum*. (See WARNINGS.)

Susceptibility Tests:

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trovafloxacin mesylate powder. The MIC values should be interpreted according to the following criteria:

For testing non-fastidious aerobic organisms

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

For testing *Haemophilus* spp.[a]:

MIC (µg/mL)	Interpretation[b]
≤ 1.0	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)[1]
[b] The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[c]:

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

[c] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.

For testing *Neisseria gonorrhoeae*[d]:

MIC (µg/mL)	Interpretation
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

[d] These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement[1].

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trovafloxacin mesylate powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)
Escherichia coli ATCC 25922	0.004-0.016
Staphylococcus aureus ATCC 29213	0.008-0.03
Pseudomonas aeruginosa ATCC 27853	0.25-2.0
Enterococcus faecalis ATCC 29212	0.06-0.25
Haemophilus influenzae[e] ATCC 49247	0.004-0.016
Streptococcus pneumoniae[f] ATCC 49619	0.06-0.25
Neisseria gonorrhoeae[g] ATCC 49226	0.004-0.016

[e] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM[1].

[f] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

[g] This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement[1]

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with trovafloxacin mesylate equivalent to 10 µg trovafloxacin to test the susceptibility of microorganisms to trovafloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a trovafloxacin mesylate disk (equivalent to 10 µg trovafloxacin) should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing non-fastidious aerobic organisms:

Zone Diameter (mm)	Interpretation

≥ 17	Susceptible (S)
14-16	Intermediate (I)
≤ 13	Resistant (R)

For testing *Haemophilus* spp.[h]:

Zone Diameter (mm)	Interpretation[i]
≥ 22	Susceptible (S)

[h] These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM[2].

[i] The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[j]:

Zone Diameter (mm)	Interpretation
≥ 19	Susceptible (S)
18-16	Intermediate (I)
≤ 15	Resistant (R)

[j] These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2

For testing *Neisseria gonorrhoeae*[k]:

Zone Diameter (mm)	Interpretation
≥ 37	Susceptible (S)
34-36	Intermediate (I)
≤ 33	Resistant (R)

[k] These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement[2] incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trovafloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the trovafloxacin mesylate equivalent to 10-μg trovafloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter Range (mm)
Escherichia coli ATCC 25922	29-36
Staphylococcus aureus ATCC 25923	29-35
Pseudomonas aeruginosa ATCC 27853	21-27
Haemophilus influenzae[l] ATCC 49247	32-39
Streptococcus pneumoniae[m] ATCC 49619	25-32
Neisseria gonorrhoeae[n] ATCC 49226	42-55

[l] This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM[2].

[m] This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

[n] This quality control range is only applicable to tests performed by disk diffusion using GC agar base and 1% defined growth supplement[2].

Anaerobic techniques: For anaerobic bacteria, the susceptibility to trovafloxacin as MICs can be determined by standardized test methods[3]. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized trovafloxacin mesylate powder should provide the following MIC values:

Microorganism	MIC[p] (µg/mL)
Bacteroides fragilis ATCC 25285	0.125-0.5
Bacteroides thetaiotaomicron ATCC 29741	0.25-1.0
Eubacterium lentum ATCC 43055	0.25-1.0

[p] These quality control ranges were derived from tests performed in the broth formulation of Wilkins-Chalgren agar.

INDICATIONS AND USAGE

TROVAN is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION)**

Nosocomial pneumonia caused by *Escherichia coli, Pseudomonas aeruginosa, Haemophilus influenzae, or Staphylococcus aureus.* As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

Community acquired pneumonia caused by *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae, Moraxella catarrhalis, Legionella pneumophila* or *Chlamydia pneumoniae.*

Acute bacterial exacerbation of chronic bronchitis caused by *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Staphylococcus aureus,* or *Haemophilus parainfluenzae.*

Acute sinusitis caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Complicated intra-abdominal infections, including post-surgical infections caused by *Escherichia coli, Bacteroides fragilis,* viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Peptostreptococcus* species or *Prevotella* species.

Gynecologic and pelvic infections including endomyometritis, parametritis, septic abortion and post-partum infections caused by *Escherichia coli, Bacteroides fragilis,* viridans group streptococci, *Enterococcus faecalis, Streptococcus agalactiae, Peptostreptococcus* species, *Prevotella* species or *Gardnerella vaginalis.*

Prophylaxis of infection associated with elective colorectal surgery, vaginal and abdominal hysterectomy.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus, Streptococcus pyogenes* or *Streptococcus agalactiae.*

Complicated skin and skin structure infections, including diabetic foot infections, caused by *Staphylococcus aureus, Streptococcus agalactiae, Pseudomonas aeruginosa, Enterococcus faecalis, Escherichia coli,* or *Proteus mirabilis.* **NOTE**: TROVAN has not been studied in the treatment of osteomyelitis. The safety and efficacy of TROVAN given for >4 weeks have not been studied. (See **PRECAUTIONS: General**)

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli.*

Chronic bacterial prostatitis caused by *Escherichia coli, Enterococcus faecalis or Staphylococcus epidermidis.*

Uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females caused by *Neisseria gonorrhoeae.* (See **WARNINGS.**)

Cervicitis due to *Chlamydia trachomatis.* **NOTE:** In males with nongonococcal urethritis TROVAN was somewhat less effective than doxycycline.

Pelvic inflammatory disease (mild to moderate) caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis.*

CONTRAINDICATIONS

TROVAN is contraindicated in persons with a history of hypersensitivity to trovafloxacin, alatrofloxacin, quinolone antimicrobial agents or any other components of these products.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF TROVAFLOXACIN IN PEDIATRIC POPULATIONS LESS THAN 18 YEARS OF AGE, PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.)

As with other members of the quinolone class, trovafloxacin has caused arthropathy and/or chondrodysplasia in immature rats and dogs. The significance of these findings to humans is unknown. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure and psychosis have been reported in patients receiving quinolones. Quinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia,

depression, nightmares and insomnia. These reactions may occur following the first dose. If these reactions occur in patients receiving trovafloxacin or alatrofloxacin, the drug should be discontinued and appropriate measures instituted. (See PRECAUTIONS: General, Information for Patients, Drug Interactions and ADVERSE REACTIONS.)

As with other quinolones, TROVAN should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other factors that predispose to seizures. (See ADVERSE REACTIONS.)

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

TROVAN should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS.)**

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including TROVAN, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS.)**

Although not seen in TROVAN clinical trials, ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. TROVAN should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise

until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones.

Trovafloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

PRECAUTIONS

General:

Because TROVAN can cause elevations of liver function tests during or soon after prolonged therapy (i.e., ≥21 days), periodic assessment of hepatic function is advisable. The safety and efficacy of TROVAN given for >4 weeks have not been studied. (See **ADVERSE REACTIONS**)

Moderate to severe phototoxicity reactions have been observed in patients who are exposed to direct sunlight while receiving some drugs in this class. Therapy should be discontinued if phototoxicity (e.g., a skin eruption, etc.) occurs.

The safety and efficacy of TROVAN in patients with severe cirrhosis (Child-Pugh Class C) have not been studied.

Information for Patients:

Patients should be advised:

- that TROVAN Tablets may be taken without regard to meals;

- that vitamins or minerals containing iron, aluminum-, or magnesium- base antacids, antacids containing citric acid buffered with sodium citrate, or sucralfate should be taken at least two hours before or two hours after taking TROVAN Tablets. (See **Drug Interactions.**);

- that TROVAN may cause lightheadedness and/or dizziness. Dizziness and/or lightheadedness was the most common adverse reaction reported, and for females under 45 years, it was reported significantly more frequently than in other groups. The incidence of dizziness may be substantially reduced if TROVAN Tablets are taken at bedtime or with food. Patients should know how they react to trovafloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination. (See **WARNINGS** and **ADVERSE REACTIONS**);

- to discontinue treatment and inform their physician if they experience pain, inflammation or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;

- that TROVAN may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema, (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS** and **ADVERSE REACTIONS**);

- to avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds) while taking TROVAN and to discontinue therapy if phototoxicity (e.g., sunburn-like reaction or skin eruption) occurs.

Drug Interactions:

No significant interactions with theophylline, cimetidine, digoxin, warfarin or cyclosporine have been observed with TROVAN Tablets **(see CLINICAL PHARMACOLOGY)**.

Minor pharmacokinetic interactions without clinical significance have been observed with co-administration of TROVAN Tablets with caffeine, omeprazole and calcium carbonate **(see CLINICAL PHARMACOLOGY)**.

Antacids, Sucralfate, and Iron: The absorption of oral trovafloxacin is significantly reduced by the concomitant administration of some antacids containing magnesium or aluminum, citric acid/sodium citrate (Bicitra®), as well as sucralfate and iron (as ferrous ions). The above oral agents should be taken at least two hours before or two hours after oral trovafloxacin administration (see **CLINICAL PHARMACOLOGY**).

Morphine: Co-administration of intravenous morphine significantly reduces the absorption of oral trovafloxacin. Intravenous morphine should be administered at least 2 hours after oral TROVAN dosing in the fasted state and at least 4 hours after oral TROVAN is taken with

753 food. Trovafloxacin administration had no effect on the pharmacokinetics of morphine or its
754 metabolite, morphine-6-β-glucuronide. (See **CLINICAL PHARMACOLOGY**).
755
756 Alatrofloxacin should not be co-administered with any solution containing multivalent
757 cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND**
758 **ADMINISTRATION**)
759
760 **Laboratory Test Interactions:** There are no reported laboratory test interactions.
761
762 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**
763
764 Long term studies in animals to determine the carcinogenic potential of trovafloxacin or
765 alatrofloxacin have not been conducted.
766
767 Trovafloxacin was not mutagenic in the Ames Salmonella reversion assay
768 or CHO/HGPRT mammalian cell gene mutation assay and it was not clastogenic in
769 mitogen-stimulated human lymphocytes or mouse bone marrow cells. A mouse
770 micronucleus test conducted with alatrofloxacin was also negative. The positive response
771 observed in the *E. coli* bacterial mutagenicity assay may be due to the inhibition of DNA
772 gyrase by trovafloxacin.
773
774 Trovafloxacin and alatrofloxacin did not affect the fertility of male or female rats at oral and
775 IV doses of 75 mg/kg/day and 50 mg/kg/day, respectively. These doses are 15 and 10
776 times the recommended maximum human dose based on mg/kg or approximately 2 times
777 based on mg/m^2. However, oral doses of trovafloxacin at 200 mg/kg/day (40 times the
778 recommended maximum human dose based on mg/kg or about 6 times based on mg/m^2)
779 were associated with increased preimplantation loss in rats.
780
781 **Pregnancy: Teratogenic Effects. Pregnancy Category C:**
782
783 An increase in skeletal variations was observed in rat fetuses after daily oral 75 mg/kg
784 maternal doses of trovafloxacin (approximately 15 times the highest recommended human
785 dose based on mg/kg or twice the based upon body surface area) were administered during
786 organogenesis. However, fetal skeletal variations were not observed in rats dosed orally with
787 15 mg/kg trovafloxacin. Evidence of fetotoxicity (increased perinatal morality and decreased
788 body weights) was also observed in rats at 75 mg/kg. Daily oral doses of trovafloxacin at 45
789 mg/kg (approximately 9 times the highest recommended human dose based on mg/kg or
790 2.7 times based upon body surface area) in the rabbit were not associated with an increased
791 incidence of fetal skeletal variations or malformations.
792
793 An increase in skeletal variations and malformations was observed in rat fetuses after daily
794 intravenous doses of alatrofloxacin at ≥20 mg/kg/day (approximately 4 times the highest
795 recommended human dose based on mg/kg or 0.6 times based upon body surface area)
796 were administered to dams during organogenesis. In the rabbit, an increase in fetal skeletal
797 malformations was also observed when 20 mg/kg/day (approximately equal to the highest
798 recommended human dose based upon body surface area) of alatrofloxacin was given
799 intravenously during the period of organogenesis. Intravenous dosing of alatrofloxacin at
800 6.5 mg/kg in the rat or rabbit was not associated with an increased incidence of skeletal
801 variations or malformations. Fetotoxicity and fetal skeletal malformations have been
802 associated with other quinolones.
803
804 Oral doses of trovafloxacin >5mg/kg were associated with an increased
805 gestation time in rats and several dams at 75 mg/kg experienced uterine dystocia.
806

There are no adequate and well-controlled studies in pregnant women. TROVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**)

Nursing Mothers:
Trovafloxacin is excreted in human milk and was found in measurable concentrations in the breast milk of lactating subjects (See **CLINICAL PHARMACOLOGY, Distribution**).

Because of the potential for unknown effects from trovafloxacin in nursing infants from mothers taking trovafloxacin, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
The safety and effectiveness of trovafloxacin in pediatric populations less than 18 years of age have not been established. Quinolones, including trovafloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS**)

Geriatric Use:
In multiple-dose clinical trials of trovafloxacin, 27% of patients were ≥ 65 years of age and 12% of patients were ≥ 75 years of age. The overall incidence of drug-related adverse reactions, including central nervous system and gastrointestinal side effects, was less in the ≥65 year group than the other age groups.

ADVERSE REACTIONS
Over 6000 patients have been treated with TROVAN in multidose clinical efficacy trials worldwide.

In TROVAN studies the majority of adverse reactions were described as mild in nature (over 90% were described as mild or moderate). TROVAN was discontinued for adverse events thought related to drug in 5% of patients (dizziness 2.4%, nausea 1.9%, headache 1.1%, and vomiting 1.0%).

Trovan® Drug-Related Adverse Reactions (frequency ≥1%) in Multiple-Dose Clinical Trials

	100 mg oral qd (N=1536)	200 mg oral qd (N=3259)	200 mg IV→ 200 mg oral qd (N=634)	300 mg IV→ 200 mg oral qd (N=623)
Dizziness	3%	11%	2%	2%
Lightheadedness	2%	4%	2%	<1%
Nausea	4%	8%	5%	4%
Headache	4%	5%	5%	1%
Vomiting	<1%	3%	1%	3%
Diarrhea	2%	2%	2%	2%
Abdominal pain	<1%	1%	1%	0%
Application/ injection/ insertion site reaction	n/a	n/a	5%	2%
Vaginitis	1%	1%	<1%	<1%

Pruritus	<1%	<1%	2%	2%
Rash	<1%	<1%	2%	2%

Dizziness/lightheadedness on TROVAN is generally mild, lasts for a few hours following a dose, and in most cases, resolves with continued dosing. The incidence of dizziness and lightheadedness in TROVAN patients over 65 years is 3.1% and 0.6%, respectively. (See **PRECAUTIONS: Information for Patients**)

TROVAN appears to have a low potential for phototoxicity. In clinical trials with TROVAN, only mild, treatment-related phototoxicity was observed in less than 0.03% (2/7096) of patients.

Additional reported drug-related events in clinical trials (remotely, possibly, probably or unknown) that occurred in <1% of TROVAN-treated patients are:

APPLICATION/INJECTION/INCISION/INSERTION SITE:
Application/incision/injection/insertion site device complications, inflammation, pain, edema

AUTONOMIC NERVOUS: flushing, increased sweating, dry mouth, cold clammy skin, increased saliva

CARDIOVASCULAR: peripheral edema, chest pain, thrombophlebitis, hypotension, palpitation, periorbital edema, hypertension, syncope, tachycardia, angina pectoris, bradycardia, peripheral ischemia, edema, dizziness postural

CENTRAL & PERIPHERAL NERVOUS SYSTEM: confusion, paresthesia, vertigo, hypoesthesia, ataxia, convulsions, dysphonia, hypertonia, migraine, involuntary muscle contractions, speech disorder, encephalopathy, abnormal gait, hyperkinesia, hypokinesia, tongue paralysis, abnormal coordination, tremor, dyskinesia

GASTROINTESTINAL: abdominal pain, altered bowel habit, constipation, diarrhea-*Clostridium difficile*, dyspepsia, flatulence, loose stools, gastritis, dysphagia, increased appetite, gastroenteritis, rectal disorder, colitis, pseudomembranous colitis, enteritis, eructation, gastrointestinal disorder, melena, hiccup

ORAL CAVITY: gingivitis, stomatitis, altered saliva, tongue disorder, tongue edema, tooth disorder, chelitis, halitosis

GENERAL/OTHER: fever, fatigue, pain, asthenia, moniliasis, hot flushes, back pain, chills, infection(bacterial, fungal), malaise, sepsis, alcohol intolerance, allergic reaction, anaphylactoid reaction, drug(other) toxicity/reaction, weight increase, weight decrease

HEMATOPOIETIC: anemia, granulocytopenia, hemorrhage unspecified, leukopenia, prothrombin decreased, thrombocythemia, thrombocytopenia

LIVER/BILIARY: increased hepatic enzymes, hepatic function abnormal, bilirubinemia, discolored feces, jaundice

METABOLIC/NUTRITIONAL: hyperglycemia, thirst

MUSCULOSKELETAL: arthralgia, muscle cramps, myalgia, muscle weakness, skeletal pain, tendinitis, arthropathy

PSYCHIATRIC: anxiety, anorexia, agitation, nervousness, somnolence, insomnia, depression, amnesia, concentration impaired, depersonalization, dreaming abnormal, emotional lability, euphoria, hallucination, impotence, libido decreased-male, paroniria, thinking abnormal

REPRODUCTIVE: Female: leukorrhea, menstrual disorder;
Male: balanoposthitis

RESPIRATORY: dyspnea, rhinitis, sinusitis, bronchospasm, coughing, epistaxis, respiratory insufficiency, upper respiratory tract infection, respiratory disorder, asthma, hemoptysis, hypoxia, stridor

SKIN/APPENDAGES: pruritus, pruritus ani, skin disorder, skin ulceration, angioedema, dermatitis, dermatitis fungal, photosensitivity skin reaction, seborrhea, skin exfoliation, urticaria

SPECIAL SENSES: taste perversion, eye pain, abnormal vision, conjunctivitis, photophobia, conjuctival hemorrhage, hyperacusis, scotoma, tinnitus, visual field defect, diplopia, xerophthalmia

URINARY SYSTEM: dysuria, face edema, micturition frequency, nephritis interstitial, renal failure acute, renal function abnormal, urinary incontinence

LABORATORY CHANGES: Changes in laboratory parameters, without regard to drug relationship, occurring in ≥1% of TROVAN treated patients were: Decreased hemoglobin and hematocrit; increased platelets; decreased and increased WBC; eosinophilia; increased ALT (SGPT), AST (SGOT), and alkaline phosphatase; decreased protein and albumin; increased BUN and creatinine; decreased sodium; and bicarbonate. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

The incidence and magnitude of liver function abnormalities with TROVAN were the same as comparator agents except in the only study in which oral TROVAN was administered for 28 days. In this study (chronic bacterial prostatitis) nine percent (13/140) of TROVAN-treated patients experienced elevations of serum transaminases (AST and/or ALT) of ≥3 times the upper limit of normal. These liver function test abnormalities generally developed at the end of, or following completion of, the planned 28-day course of therapy, but were not associated with concurrent elevations of related laboratory measures of hepatic function (such as serum bilirubin, alkaline phosphatase, or lactate dehydrogenase). Patients were asymptomatic with these abnormalities, which generally returned to normal within 1-2 months after discontinuation of therapy. (See **PRECAUTIONS - General**.)

OVERDOSAGE

Trovafloxacin has a low order of acute toxicity. The minimum lethal oral dose in mice and rats was 2000 mg/kg or greater. The minimum lethal i.v. dose for the prodrug, alatrofloxacin, was 50-125 mg/kg for mice and greater than 75 mg/kg for rats. Clinical signs observed included decreased activity and respiration, ataxia, ptosis, tremors and convulsions.

In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given symptomatic and supportive treatment. Adequate hydration should be maintained. Trovafloxacin is not efficiently removed from the body by hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended dosage for TROVAN Tablets or TROVAN I.V. for the treatment of infections is described in the table below. Doses of TROVAN are administered once every 24 hours.

Oral doses should be administered at least two hours before or two hours after antacids containing magnesium or aluminum, as well as sucralfate, citric acid buffered with sodium citrate (e.g., Bicitra®) and metal cations (e.g., ferrous sulfate).

Intravenous morphine should be administered at least 2 hours after oral TROVAN dosing in the fasted state and at least 4 hours after oral TROVAN is taken with food.

When switching from intravenous to oral dosage administration, for comparable dosages, no adjustment is necessary. Patients whose therapy is started with TROVAN I.V. may be switched to TROVAN Tablets when clinically indicated at the discretion of the physician.

TROVAN I.V. (alatrofloxacin mesylate injection) should only be administered by INTRAVENOUS infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Single-use vials require dilution prior to administration. (See **PREPARATION FOR ADMINISTRATION**.)

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DOSAGE GUIDELINES		
INFECTION*/LOCATION AND TYPE	DAILY UNIT DOSE AND ROUTE OF ADMINISTRATION	TOTAL DURATION
Nosocomial Pneumonia (See NOTE 1 below.)	300 mg I.V. followed by 200 mg oral	10-14 days
Community Acquired Pneumonia	200 mg oral or 200 mg I.V. followed by 200 mg oral	7-14 days
Acute Bacterial Exacerbation of Chronic Bronchitis	100 mg oral	7-10 days
Acute Sinusitis	200 mg oral	10 days
Complicated Intra-Abdominal Infections, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Gynecologic and Pelvic Infections	300 mg I.V. followed by 200 mg oral	7-14 days
Surgical Prophylaxis - Elective Colorectal Surgery (See NOTE 2 below.)	200 mg I.V. or oral	Single intravenous or oral dose within 30 min. to 4 hours before surgery
Surgical Prophylaxis - Elective Abdominal and Vaginal Hysterectomy (See NOTE 2 below.)	200 mg I.V. or oral	Single intravenous or oral dose within 30 min. to 4 hours before surgery
Skin and Skin Structure Infections, Uncomplicated	100 mg Oral	7-10 days
Skin and Skin Structure Infections, Complicated, including diabetic foot infections	200 mg oral or 200 mg I.V. followed by 200 mg oral	10-14 days
Uncomplicated Urinary Tract Infections (cystitis)	100 mg oral	3 days
Chronic Bacterial Prostatitis	200 mg oral	28 days
Uncomplicated Urethral Gonorrhea Males; Endocervical and Rectal Gonorrhea in Females	100 mg oral	Single Dose
Cervicitis due to *Chlamydia trachomatis*	200 mg oral	5 days
Pelvic Inflammatory Disease (mild to moderate)	200 mg oral	14 days

970 * due to the designated pathogens (See **INDICATIONS AND USAGE**)
971
972
973 NOTE 1: As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or
974 presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam
975 may be clinically indicated.
976
977 NOTE 2: In patients where surgical prophylaxis with oral TROVAN is indicated, Bicitra®
978 should not be given within 2 hours. (See **PRECAUTIONS: Drug Interactions**)
979
980 The safety and efficacy of TROVAN use for >4 weeks have not been studied. (See
981 **PRECAUTIONS.**)
982
983 **IMPAIRED RENAL FUNCTION**: No adjustment in the dosage of TROVAN is necessary in
984 patients with impaired renal function. Trovafloxacin is eliminated primarily by biliary
985 excretion. Trovafloxacin is not efficiently removed from the body by hemodialysis.
986

CHRONIC HEPATIC DISEASE (cirrhosis): The following table provides dosing guidelines for patients with mild or moderate cirrhosis (Child-Pugh Class A and B). There are no data in patients with severe cirrhosis (Child-Pugh Class C).

INDICATED DOSE (Normal hepatic function)	CHRONIC HEPATIC DISEASE DOSE
300 mg i.v.	200 mg i.v.
200 mg i.v. or oral	100 mg i.v. or oral.
100 mg oral	100 mg oral

INTRAVENOUS ADMINISTRATION

AFTER DILUTION WITH AN APPROPRIATE DILUENT TROVAN I.V. SHOULD BE ADMINISTERED BY INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION SHOULD BE AVOIDED.

TROVAN I.V. is supplied in single-use vials containing a concentrated solution of alatrofloxacin mesylate in Water for Injection (equivalent of 200 mg or 300 mg as trovafloxacin). Each mL contains alatrofloxacin mesylate equivalent to 5 mg trovafloxacin. (See **HOW SUPPLIED** for container sizes.) THESE TROVAN I.V. SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION. This parenteral drug product should be inspected visually for discoloration and particulate matter prior to dilution and administration. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final parenteral solution.

PREPARATION OF ALATROFLOXACIN MESYLATE INJECTION FOR ADMINISTRATION

The intravenous dose should be prepared by aseptically withdrawing the appropriate volume of concentrate from the vials of TROVAN I.V. This should be diluted with a suitable intravenous solution to a final concentration of 1-2 mg/mL. (See **Compatible Intravenous Solutions**.) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

Since the vials are for single-use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of alatrofloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to TROVAN I.V. in single-use vials or infused simultaneously through the same intravenous line.

If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of TROVAN I.V. with an infusion solution compatible with TROVAN I.V. and with any other drug(s) administered via this common line.

If TROVAN I.V. is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

The desired dosage of TROVAN I.V. may be prepared according to the following chart:

DOSAGE STRENGTH (mg) (trovafloxacin equivalent)	VOLUME TO WITHDRAW (mL)	DILUENT VOLUME (mL)	TOTAL VOLUME (mL)	INFUSION CONC (mg/mL)
100 mg	20	30	50	2
100 mg	20	80	100	1
200 mg	40	60	100	2
200 mg	40	160	200	1
300 mg	60	90	150	2
300 mg	60	240	300	1

For example, to prepare a 200 mg dose at an infusion concentration of 2 mg/mL (as trovafloxacin), 40 mL of TROVAN I.V. is withdrawn from a vial and diluted with 60 mL of a compatible intravenous fluid to produce a total infusion solution volume of 100 mL.

Compatible Intravenous Solutions:

5% Dextrose Injection, USP
0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.2% Sodium Chloride Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP

Stability of TROVAN I.V. as supplied:
When stored under recommended conditions, TROVAN I.V., as supplied in ~~(20 mL)~~ 40 mL or 60 mL vials, is stable through the expiration date printed on the label.

Stability of TROVAN I.V. Following Dilution:
TROVAN I.V., when diluted with the following intravenous solutions to concentrations of 0.5 to 2.0 mg/mL (as trovafloxacin), is physically and chemically stable for up to 7 days when refrigerated or up to 3 days at room temperature stored in glass bottles or plastic (PVC type) intravenous containers.

HOW SUPPLIED

Tablets
TROVAN (trovafloxacin mesylate) Tablets are available as blue, film-coated tablets. The 100 mg tablets are round and contain trovafloxacin mesylate equivalent to 100 mg trovafloxacin. The 200 mg tablets are modified oval-shaped and contain trovafloxacin mesylate equivalent to 200 mg trovafloxacin.

TROVAN Tablets are packaged and in unit dose blister strips in the following configurations:

100-mg tablets: color: blue; shape: round
debossing: "PFIZER" on side 1 and "378" on side 2
Bottles of 30 (NDC 0049-3780-30)
Unit Dose/ 40 tablets (NDC 0049-3780-43)

200-mg tablets: color: blue; shape: modified oval
debossing: "PFIZER" on side 1 and "379" on side 2
Bottles of 30 (NDC 0049-3790-30)
Unit Dose/ 40 tablets (NDC 0049-3790-43)

Storage
TROVAN Tablets should be stored at 15 °C to 30 °C (59 °F to 86 °F) in well-closed containers.

Injection
TROVAN is also available for intravenous administration as the prodrug, TROVAN I.V. (alatrofloxacin mesylate injection), in the following configurations:
Single-use vials containing a clear, colorless to pale-yellow concentrated solution of alatrofloxacin mesylate equivalent to 5 mg trovafloxacin/mL.

5 mg/mL, 40 mL, 200 mg
Unit dose package (NDC 0049-3890-28)

5 mg/mL, 60 mL, 300 mg
Unit dose package (NDC 0049-3900-28)

Storage
TROVAN I.V. should be stored at 15 °C to 30 °C (59 °F to 86 °F). Protect From Light. Do Not Freeze.

ANIMAL PHARMACOLOGY:

Quinolones have been shown to cause arthropathy in immature animals.

Arthropathy and chondrodysplasia were observed in immature animals given trovafloxacin (See **WARNINGS**).

At doses from 10 to 15 times the human dose base on a mg/kg or approximately 3 to 5 times based on mg/m^2, trovafloxacin has been shown to cause arthropathy in immature rats and dogs. In addition, these drugs are associated with an increased incidence of chondrodysplasia in rats compared to controls. There is no evidence of arthropathies in fully mature rats and dogs at doses from 40 or 10 times the human dose based on mg/kg or approximately 5 times based on mg/m^2 for a 6 month exposure period.

Unlike some other members of the quinolone class, crystalluria and ocular toxicity were not observed in chronic safety studies with rats or dogs with either trovafloxacin or its prodrug, alatrofloxacin.

Quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal antiinflammatory drugs (NSAIDS). Neither trovafloxacin administered orally at 500 mg/kg, nor alatrofloxacin administered intravenously at 75 mg/kg, showed an increase in measures of seizure activity in mice at doses when used in combination with the active metabolite of the NSAID, fenbufen.

As with other members of the quinolone class, trovafloxacin at doses 5 to 10 times the human dose based on mg/kg or 1 to 5 times the human dose based on mg/m^2 produces testicular degeneration in rats and dogs dosed for 6 months.

At a dose of trovafloxacin 10 times the highest human dose based on mg/kg or approximately 5 times based on mg/m^2, elevated liver enzyme levels which correlated with centrilobar hepatocellular vacuolar degeneration and necrosis were observed in dogs in a 6 month study. A subsequent study demonstrated reversibility of these effects when trovafloxacin was discontinued.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis

Patients with clinically documented acute bacterial exacerbation of chronic bronchitis participated in a randomized, double blind, multicenter trial comparing oral trovafloxacin (100mg once daily) with oral clarithromycin (500mg twice daily) for 7 days. The clinical success rate (cure + improvement, with no need for further antibiotic therapy) at the End of Treatment was 89% (181/203) and 85% (160/188) for trovafloxacin and clarithromycin respectively. The clinical success rate at the End of Study (Day 28) was 80% (158/197) and 74% (131/178) for trovafloxacin and clarithromycin respectively.

The following are the clinical success rates for the clinically evaluable groups by pathogen:

	End of Treatment		End of Study	
Pathogen	Trovafloxacin 100 mg	Clarithromycin 500 mg BID	Trovafloxacin 100 mg	Clarithromycin 500 mg BID
H. influenzae	92% (24/26)	89% (16/18)	92% (24/26)	44% (7/16)*
M. catarrhalis	78% (14/18)	80% (16/20)	71% (12/17)	74% (14/19)
S. pneumoniae	100% (7/7)	91% (10/11)	86% (6/7)	91% (10/11)
H. parainfluenzae	100% (6/6)	86% (6/7)	100% (6/6)	86% (6/7)
S.aureus	93% (13/14)	83% (10/12)	85% (11/13)	75% (9/12)

*p= 0.001

Of the above patients with clinical failure at end of treatment or study, no trovafloxacin and 2 clarithromycin patients (both *H.influenzae*) had positive post treatment cultures for the baseline pathogen. There was no emergence of resistance in either treatment group. Fewer patients required hospitalization during study (Day 1-35) in the trovafloxacin group (3/210) than in the clarithromycin group (10/200), p=0.039.

Hospitalized Community Acquired Pneumonia

Adult patients with clinically and radiologically documented community acquired pneumonia, requiring hospitalization and initial intravenous therapy, participated in two randomized, multicenter, double-blind, double-dummy trials. The first trial compared intravenous alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg BID) plus ampicillin (500mg QID) for 2 to 7 days followed by oral ciprofloxacin (500mg BID) plus amoxicillin (500mg TID) for a total of 7 to 14 days of therapy. The second study compared intravenous alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ceftriaxone (1000mg once daily for 2 to 7 days) followed by oral cefpodoxime (400mg BID) for 7 to 14 days of total therapy with optional blinded erythromycin added to the ceftriaxone/cefpodoxime arm if an atypical pneumonia was suspected.

The clinical success rate (cure + improvement with no need for further antibiotic therapy) at the End of Treatment was 90% (311/346) and 90% (325/363) for TROVAN and the comparator agents respectively. The clinical success rate at the End of Study (Day 30) was 86% (256/299) and 85% (283/334) for TROVAN and the comparator agents respectively. All cause mortality (Day 1-35) was 2.45% (10/408) on TROVAN and 5.45% (23/422) on the comparator agents.

The following outcomes are the clinical success rates for the clinically evaluable patient groups by pathogen in these two studies:

	End of Treatment		End of Study	
Pathogen	TROVAN	Comparators	TROVAN	Comparators
S. pneumoniae	89% (63/71)	95% (62/65)	87% (55/63)	91% (50/55)
H. influenzae	97% (35/36)	94% (46/49)	90% (28/31)	94% (44/47)
M. catarrhalis	100% (8/8)	100% (4/4)	100% (6/6)	100% (4/4)
S. aureus	100% (8/8)	93% (13/14)	100% (6/6)	91% (10/11)
K. pneumoniae	100% (3/3)	89% (8/9)	100% (3/3)	86% (6/7)
L. pneumophila	77% (10/13)	86% (12/14)	75% (9/12)	86% (12/14)
M. pneumoniae	100% (20/20)	87% (13/15)	94% (17/18)	79% (11/14)
C. pneumoniae	75% (6/8)	100% (18/18)	67% (4/6)	94% (16/17)

Of the above patients with clinical failure at end of treatment or study, only one alatrofloxacin patient (*H. influenzae + S .pneumoniae*) and one ceftriaxone + erythromycin patient (*Legionella*) had a microbiologically confirmed persistent pathogen at the time of failure with no emergence of resistance in either study.

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia, participated in a randomized, multicenter, double-blind, double-dummy trial comparing intravenous alatrofloxacin (300mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg BID) for 2 to 7 days followed by oral ciprofloxacin (750mg BID) for a total of 7 to 14 days of therapy with optional blinded clindamycin or metronidazole added to the ciprofloxacin arm if an anaerobic pneumonia was suspected. In subjects with documented Pseudomonas infection or methicillin-resistant S. aureus, aztreonam or vancomycin, respectively, could have been added to either treatment regimen.

The clinical success rate (cure + improvement with no need for further antibiotic therapy) at the End of Treatment was 77% (68/88) and 78% (79/101) for TROVAN and ciprofloxacin respectively. The clinical success rate at the End of Study (Day 30) was 69% (50/72) and 68% (54/79) for TROVAN and ciprofloxacin respectively.

The following outcomes are the clinical success rates for the clinically evaluable patient groups by pathogen:

	End of Treatment		End of Study	
Pathogen	TROVAN	Ciprofloxacin	TROVAN	Ciprofloxacin
P. aeruginosa	67% (10/15)	55% (6/11)	62% (8/13)	25% (2/8)
H. influenzae	88% (7/8)	89% (8/9)	83% (5/6)	86% (6/7)
E. coli	71% (5/7)	80% (4/5)	50% (3/6)	80% (4/5)
S. aureus	64% (7/11)	80% (8/10)	50% (4/8)	67% (4/6)

Of the above patients with clinical failure at end of treatment or study, two alatrofloxacin patients (*S.aureus*, *P.aeruginosa*) and 4 ciprofloxacin patients (all *P.aeruginosa*) had a microbiologically confirmed persistent pathogen at the time of failure. Three of the 4 ciprofloxacin patients with clinical failure and persistence had emergence of resistance with none on alatrofloxacin.

Complicated Intra-Abdominal Infections

Patients hospitalized with clinically-documented, complicated intra-abdominal infections, including post-surgical infections participated in a randomized, double-blind, multicenter trial comparing intravenous alatrofloxacin (300 mg once daily) followed by oral trovafloxacin (200 mg once daily) to intravenous imipenem/cilastatin (1g q8h) followed by oral amoxicillin/clavulanic acid (500 mg TID) for a maximum of 14 days of therapy. The clinical success rate (cure + improvement) at the End of Treatment was 88% (136/155) and 86% (122/142) for alatrofloxacin→trovafloxacin and imipenem/cilastatin→amoxicillin/clavulanic acid, respectively. The clinical success rate at the End of Study (Day 30) was 83% (129/156) and 84% (127/152) for alatrofloxacin→trovafloxacin and imipenem/cilastatin→amoxicillin/clavulanic acid respectively.

The following are the clinical success rates for the clinically-evaluable patient groups by pathogen:

	End of Treatment		End of Study	
Pathogen	TROVAN	Imipenem/Cila Amox/Clav	TROVAN	Imipenem/Cila Amox/Clav
E. coli	94% (72/77)	90% (52/58)	86% (66/77)	86% (51/59)

Bacteroides fragilis	97% (30/31)	82% (28/34)	84% (26/31)	75% (27/36)
viridans group streptococci	90% (18/20)	83% (19/23)	90% (18/20)	78% (18/23)
Pseudomonas aeruginosa	94% (15/16)	82% (14/17)	88% (14/16)	83% (15/18)
Klebsiella pneumoniae	80% (12/15)	71% (10/14)	67% (10/15)	71% (10/14)
Peptostreptococcus spp.	86% (12/14)	88% (7/8)	79% (11/14)	75% (6/8)
Prevotella spp.	77% (10/13)	50% (2/4)	77% (10/13)	60% (3/5)

Of patients with a baseline pathogen and a clinical response of failure at the End of Study, 9 of 26 on TROVAN and 10 of 21 on imipenem/cilastatin had microbiologically-confirmed persistence of the baseline pathogen with no emergence of resistance in either group.

CAUTION: FEDERAL (USA) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

REFERENCES:

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fourth Edition; Approved Standard, NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Villanova, PA, January, 1997.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Sixth Edition; Approved Standard, NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Villanova, PA, January 1997.

3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria--Third Edition; Approved Standard, NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December, 1993.

TROVAN is manufactured and distributed by:

Roerig
Division of Pfizer Inc., NY, NY 10017

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Of patients with a baseline pathogen and a clinical response of failure at the End of Study, 9 of 26 on TROVAN and 10 of 21 on imipenem/cilastatin had microbiologically-confirmed persistence of the baseline pathogen with no emergence of resistance in either group.

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